SHORT REPORT

Hippocampal volume and subcortical white matter lesions in late life depression: comparison of early and late onset depression

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Background: Reduced hippocampal volume and increased prevalence of subcortical white matter lesions are associated with both recurrent early onset depression (EOD) and late onset depression (LOD). It is not clear whether these two factors differentially affect the age of onset of first depression. Therefore, we wished to investigate the relationship between age of first depression onset and hippocampal volume, with adjustment for subcortical white matter lesions.

Methods: MRI brain scans were used to compare hippocampal volumes and white matter lesions between age matched female patients (>60 years) with recurrent EOD and LOD and healthy controls.

Results: When comparing the three groups and adjusting for age, the Mini-Mental State Examination score, total brain volume and total hippocampal volume were significantly smaller in patients with EOD compared with controls (5.6 vs 6.1 ml; p = 0.04). The prevalence of larger subcortical white matter lesions was higher in patients with LOD compared with patients with EOD (47% vs 8%; p = 0.002). Patients with LOD did not differ in hippocampal volume from patients with EOD or from controls.

Conclusions: In late life depression, age of first depression onset may distinguish between different independent neuropathological mechanisms. A small hippocampus volume may be a neuranatomical marker of EOD depression and larger subcortical white matter lesions could be an intermediate between cerebrovascular disease and LOD.

Reduced hippocampal volume in late life depression (depression in those aged ⩾60 years) is associated with a chronic intermittent illness course.[1–4] Accordingly, older patients with recurrent early onset depression (EOD, first onset of depression before 60 years) would therefore have smaller hippocampal volumes compared with patients with late onset depression (LOD, first onset of depression at age 60 years or after) because of the longer duration of the disease. However, two recent studies showed smaller hippocampal volumes in patients with LOD compared with those with EOD.[5 6]

The latter observation could have been confounded by the increased prevalence of subcortical white matter lesions among patients with LOD[7–9] as these lesions may be related to hippocampal atrophy.[10–12] Therefore, in the current study we wished to investigate the relationship between age of onset of depression and hippocampal volume, with adjustment for subcortical white matter lesions, in elderly (⩾60 years) patients with chronic recurrent EOD and patients with LOD.

METHODS

Participants

We investigated 13 patients with EOD, 15 patients with LOD and 22 healthy controls. All study participants were female and aged 60 years or older. Unipolar EOD patients and healthy controls were taken from a sample described previously.[13] All LOD participants were inpatients who met criteria for unipolar major depression according to the *Diagnostic and statistical manual of mental disorders*, 4th edn, had an age of onset of the first depressive episode at age 60 years or older and did not have contraindications for MRI acquisition. The exclusion criteria for all EOD and LOD patients were a history of central nervous system disease, dementia, substance dependence within the past year, terminal somatic illness and a Mini-Mental State Examination (MMSE)[14] score >15. There is a relationship between the hippocampus and cognition (as measured with the MMSE in our study) but also with depression.[3] Consequently, the MMSE could possibly act as a confounder in this relation. Therefore, analysis with or without the appropriate adjustments for MMSE were made. No patients had undergone previous ECT.

The Montgomery–Åsberg Depression Rating Scale[15] was assessed at the time of the scan to measure the severity of any present depressive symptoms at that particular moment. To approximate a representative sample of the population, patients and controls with the cerebrovascular risk factors hypertension, diabetes and smoking were not excluded. At the time of the MRI acquisition, 4 (14%) patients were receiving lithium. Two independent clinical neuroradiologists examined the MRI brain scans; no gross brain abnormalities were reported in any of the participants. The ethics committee of the University Medical Centre of Utrecht approved the study. A written informed consent was obtained from all subjects after information on the study was provided.

MRI acquisition

All participants underwent brain MRI, including a T1 weighted and a T2 weighted, dual turbo spin echo scan, on a 1.5 T scanner (Philips Medical Systems, Best, The Netherlands).

Brain volumes and white matter lesions

Intracranial, total brain and hippocampal volumes were segmented as previously described.[13] Subcortical white matter lesions were counted and categorised, according to their largest diameter, as small (<3 mm) or large (>3 mm) lesions in each slice. Periventricular white matter lesions adjacent to the frontal, lateral or occipital wall of the ventricle were rated

Abbreviations: EOD, early onset depression; LOD, late onset depression; MMSE, Mini-Mental State Examination

Table 1 Demographic and clinical data, raw brain volumes and number of white matter lesions in normal controls and in those with early onset and late onset depression

	EOD (n = 13)	LOD (n = 15)	NC (n = 22)	EOD vs LOD*	EOD vs NC	LOD vs NC
Age (y)	70.38 (8.3)	72.67 (6.7)	71.05 (7.5)	p = 0.41	p = 0.81	p = 0.50
Education (y)	10.54 (4.1)	8.00 (2.3)	10.68 (3.1)	p = 0.05	p = 0.92	p = 0.02
MADRS score	9.77 (7.0)	33.93 (7.4)	4.77 (4.3)	p<0.01	p = 0.03	p<0.01
MMSE score	27.69 (1.8)	26.33 (3.2)	28.14 (1.8)	p = 0.18	p = 0.48	p = 0.03
Age at onset (y)	33.62 (8.8)	69.93 (6.4)		p<0.01		
Cerebrovascular risk factors						
Smoking (n (%))	4 (31)	4 (29)	1 (5)	p = 0.22	p = 0.04	p = 0.07
Diabetes (n (%))	1 (8)	1 (8)	0	p = 0.52	p = 0.37	p = 0.41
Hypertension (n (%))	5 (39)	4 (29)	5 (23)	p = 0.25	p = 0.18	p = 0.29
Total brain volume (ml)	1058.62 (14.3)	1031.95 (13.4)	1081.47 (11.1)	p = 0.17	p = 0.13	p<0.01
Total hippocampal volume (ml)	5.51 (0.2)	5.92 (0.2)	6.0 (0.1)	p = 0.16	p = 0.04	p = 0.65
White matter lesions						
Periventricular prevalence						
Frontal (n (%))	4 (31)	6 (40)	5 (23)	p = 0.27	p = 0.27	p = 0.19
Lateral (n (%))	4 (31)	5 (33)	6 (27)	p = 0.31	p = 0.29	p = 0.26
Occipital (n (%))	0	3 (20)	3 (14)	p = 0.14	p = 0.24	p = 0.30
Subcortical prevalence						
Small (n (%))	7 (54)	10 (67)	9 (41)	p = 0.76	p = 0.89	p = 0.35
Larger (n (%))	1 (8)	7 (47)	1 (5)	p = 0.03	p = 0.48	p<0.01

EOD, early onset depression; LOD, late onset depression; MADRS, Montgomery–Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination; NC, normal controls.
Values are mean (SD) or number (%).
*Differences in continuous variables and non-continuous variables were tested using the independent sample t test, Fisher's exact probability test and χ^2 tests. Differences in total brain and hippocampal volume were tested by analysis of variance (ANOVA), adjusting for age, MMSE and intracranial volume (total brain volume for hippocampus volume). Adding larger subcortical white matter lesions as a covariate did not change the results.

semiquantitatively (0–3) per region. This scale has been used previously.[9]

Reliability

Intraclass correlations for the left and right hippocampus were 0.94 and 0.90 and weighted κ values for grading the periventricular and subcortical white matter lesions ranged from 0.87 to 0.92.

Statistical analyses

Total brain and hippocampal volumes were normalised for head size by dividing by the intracranial volume and total brain volume, respectively. The relationship between hippocampal volume and age of onset of depression was tested by one way analysis of variance (ANOVA) with post hoc tests. Adjustments were made for age, total brain volume and MMSE score. Intracranial volume served as a covariate in the analysis of total brain volume. Secondly, subcortical white matter lesions were added to the model to assess whether the volumes across groups changed. Demographical and clinical data, and white matter lesion prevalence were analysed using the independent sample t test, χ^2 analyses and Fisher's exact test.

RESULTS

Patients with LOD had significantly fewer years of education and lower MMSE scores compared with healthy controls (table 1).

MMSE scores did not differ between the two patient subgroups. Montgomery–Åsberg Depression Rating Scale scores at the time of MRI acquisition differed significantly between the two patient subgroups and between the patient subgroups and healthy controls. Smoking was more prevalent among the patients subgroups compared with controls; hypertension and diabetes did not differ between the three subgroups.

Adjusted hippocampal volume was smaller in patients with EOD compared with controls (5.6 vs 6.1 ml; df = 44, p = 0.04) (table 1), after controlling for age, total brain volume and MMSE score.

In the same analysis, patients with LOD did not differ in adjusted hippocampal volume from patients with EOD (5.8 vs 5.6 ml; df = 44, p = 0.15) or from controls (5.8 vs 6.1 ml; df = 44, p = 0.70). Covarying for subcortical white matter lesions did not change the results.

For larger subcortical white matter lesions, the prevalence was significantly higher for patients with LOD compared with those with EOD or controls ($\chi^2 = 11.98$, df = 2, p = 0.002). The frequency of small subcortical white matter lesions did not differ between the three subgroups. The prevalence of frontal, lateral and occipital periventricular white matter lesions was not different between the three subgroups.

Total brain volume was smaller in patients with LOD compared with controls (1037.1 vs 1071.7 ml; F = 3.05, df = 44, p = 0.02) after controlling for age, intracranial volume and MMSE score. There were no significant differences in total brain volume in the other comparisons. Adding subcortical white matter lesions to the model did not change the results.

Excluding the four patients who received lithium did not change the results.

DISCUSSION

We found a reduced hippocampal volume in older EOD patients and a higher prevalence of larger subcortical white matter lesions in LOD patients compared with controls. Hippocampal volume of LOD patients did not differ from normal controls. Our findings are in line with previous reports of a smaller hippocampal volume in adult and older patients with chronic recurrent depression.[1–4]

Two studies describing decreased hippocampal volume in LOD patients but not in EOD patients included EOD patients who were substantially younger and had less depressive episodes[5 6] compared with our sample. The EOD patients in these two studies may thus have had a less severe history of depressive illness and consequently less damage to the hippocampus.

Patients with LOD in our study had a smaller total brain volume. Smaller cerebral gray matter volume, particularly in

the prefrontal cortex, has been associated with LOD.[16 17] It is not clear whether this finding is related to the subcortical lesions although one study showed such an association.[17]

We would have anticipated a lower hippocampal volume in LOD patients as they had more subcortical white matter lesions[8] but this was not the case. Given their smaller total brain volume, they had proportionally the largest hippocampal volume. This finding may suggest that the ischaemic cerebrovascular pathology in our LOD patients was not as severe as in dementia. Alternatively, the subcortical white matter lesions may not represent generalised ischaemic damage, but rather region specific subcortical white matter lesions may be necessary to cause hippocampal atrophy.[10]

Our results strengthen previous findings of different neuropathological mechanisms leading to late life depression.[18] For EOD, stress related neurotoxic factors associated with repeated episodes of depression may result in a small hippocampal volume.[19] In LOD, cerebrovascular risk factors or disease may be related to depression, probably with large subcortical white matter lesions as an intermediate.[20]

This study was limited in several aspects. Firstly, the number of patients in our sample was small, resulting in limited statistical power which may have prevented us from finding differences in hippocampal volume between patients with EOD and LOD (type II error). Secondly, we did not control for the effect of cumulative years of medication use.

Longitudinal studies, combining clinical, MRI, neuroendocrinological and neuropsychological data are needed to further elucidate the potential separate neural pathways that may lead to late life depression.

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